Complete Summary

GUIDELINE TITLE

Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America.

BIBLIOGRAPHIC SOURCE(S)

Wheat LJ, Freifeld AG, Kleiman MB, Baddley JW, McKinsey DS, Loyd JE, Kauffman CA, Infectious Diseases Society of America. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis 2007 Oct 1;45(7):807-25. [105 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Wheat J, Sarosi G, McKinsey D, Hamill R, Bradsher R, Johnson P, Loyd J, Kauffman C. Practice guidelines for the management of patients with histoplasmosis. Infectious Diseases Society of America. Clin Infect Dis 2000 Apr;30(4):688-95.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Histoplasmosis, including:
  - Acute pulmonary
  - Chronic pulmonary
  - Progressive disseminated

    - Central nervous system
- Complications from pulmonary histoplasmosis, including:
    - Pericarditis
    - Rheumatologic syndromes
    - Mediastinal lymphadenitis
    - Mediastinal granuloma
    - Mediastinal fibrosis
    - Broncholithiasis
    - Pulmonary nodules (histoplasmomas)

GUIDELINE CATEGORY

Management
Prevention
Treatment

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology
Pediatrics

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To update recommendations for treating patients with histoplasmosis

TARGET POPULATION

Patients with histoplasmosis including pregnant women, children, and immunosuppressed patients

INTERVENTIONS AND PRACTICES CONSIDERED

Management/Treatment/Prevention

1. Itraconazole and obtaining blood levels of itraconazole after 2 weeks of treatment
2. Other azoles as second-line alternatives
3. Amphotericin B deoxycholate
4. Amphotericin B lipid formulation
5. Liposomal amphotericin B
6. Corticosteroids
7. Non-steroidal anti-inflammatory therapy as indicated
8. Intravascular stents in pulmonary vessel obstruction
9. Antigen level monitoring

Refer to Table 3 in the original guideline document for information on dosages and modifications for pregnancy and children.

MAJOR OUTCOMES CONSIDERED

- Sensitivity and specificity of antigen testing
- Effectiveness of treatment including response rate, relapse rate, and mortality rate

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

For the 2007 update, the Expert Panel completed the review and analysis of data published since 1999. Computerized literature searches of PUBMED were performed. The searches of the English-language literature from 1999 to July, 2006, using the terms, histoplasmosis or *Histoplasma* focused on human studies but included a few studies from experimental models of histoplasmosis.

Literature Search

The literature search identified 858 potential articles. A few abstracts from national meetings were included. The types of studies included randomized clinical trials, open label clinical trials, retrospective case series, case reports, reports of in vitro studies and animal model experiments. Due to the limited nature of the data in many areas, the Panel made a decision to also retain high-quality reviews or background papers. Panel members were assigned sections of the guideline and reviewed the relevant literature.

Limitations in the Literature

Review of the literature revealed a paucity of clinical trials evaluating the newer agents in histoplasmosis. Most data came from cohort studies, case series, small nonrandomized clinical trials or case reports.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Quality of Evidence

I. Evidence from ≥1 properly randomized, controlled trial
II. Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series studies; or from dramatic results from uncontrolled experiments
III. Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

In evaluating the evidence regarding the management of histoplasmosis, the Panel followed a process used in the development of other Infectious Diseases Society of America (IDSA) guidelines. The process included a systematic weighting of the quality of the evidence and the grade of recommendation (see the "Rating Scheme for the Strength of the Evidence" and the "Rating Scheme for the Strength of the Recommendations" fields).

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Infectious Diseases Society of America (IDSA) Standards and Practice Guidelines Committee (SPGC) convened experts in the management of patients with histoplasmosis. The Panel members are listed in Appendix 1 of the original guideline document.

Consensus Development Based on Evidence

The Panel met on six occasions via teleconference to complete the work of the guideline. The purpose of the teleconferences was to discuss the questions to be addressed, make writing assignments and discuss recommendations. All members of the panel participated in the preparation and review of the draft guideline. Feedback from external peer reviews was obtained.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of Recommendation:

A. Good evidence to support a recommendation for use
B. Moderate evidence to support a recommendation for use
C. Poor evidence to support a recommendation

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

All members of the panel participated in the preparation and review of the draft guideline. Feedback from external peer reviews was obtained. The guideline was reviewed and approved by the Infectious Diseases Society of America (IDSA) Standards and Practice Guidelines Committee and the Board of Directors prior to dissemination.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions of the levels of evidence (I-III) and grades of recommendation (A-C) are repeated at the end of the "Major Recommendations" field.

Indications for Antifungal Therapy

Definite Indication, Proven or Probable Efficacy

- Acute diffuse pulmonary, moderately severe or severe symptoms
- Chronic cavitary pulmonary
- Progressive disseminated
- Central nervous system infection

Uncertain Indication, Unknown Efficacy

- Acute focal pulmonary, asymptomatic or mild symptoms persistent >1 month
- Mediastinal lymphadenitis
- Mediastinal granuloma
- Inflammatory syndromes, treated with corticosteroids

Not Recommended, Unknown Efficacy or Ineffective

- Mediastinal fibrosis
- Pulmonary nodule
- Broncholithiasis
- Presumed ocular histoplasmosis syndrome

What Is the Treatment for Acute and Chronic Pulmonary Histoplasmosis?

Moderately Severe To Severe Acute Pulmonary Histoplasmosis

1. Lipid formulation of amphotericin B, 3.0 to 5.0 mg/kg/day (d) intravenously (IV), for one to two weeks, followed by itraconazole, 200 mg 3 times daily for 3 days and then 200 mg twice daily, for a total of 12 weeks is recommended **(AIII)**.
2. The deoxycholate formulation of amphotericin B 0.7 to 1.0 mg/kg/d is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity **(AIII)**.
3. Methylprednisolone, 0.5 to 1.0 mg/kg/d given intravenously, during the first 1 to 2 weeks of antifungal therapy is recommended for patients who develop respiratory complications, including hypoxemia or significant respiratory distress **(BIII)**.

Mild to Moderate Acute Pulmonary Histoplasmosis

4. Treatment is usually unnecessary **(AIII)**. Itraconazole, 200 mg 3 times daily for 3 days and then 200 mg once or twice daily, for 6 to 12 weeks is recommended in those patients who continue to have symptoms for longer than a month **(BIII)**.

Chronic Cavitary Pulmonary Histoplasmosis

5. Itraconazole, 200 mg 3 times daily for 3 days and then once or twice daily for at least one year is recommended, but some prefer 18 to 24 months in view of the risk for relapse **(AII)**.
6. Blood levels of itraconazole should be obtained after the patient has been on this agent for at least two weeks to ensure adequate drug exposure **(AIII)**.

What Is the Treatment for the Complications from Pulmonary Histoplasmosis (e.g., pericarditis, arthritis/erythema nodosum, mediastinal lymphadenitis, mediastinal granuloma, mediastinal fibrosis, broncholithiasis, and pulmonary nodule)?

Pericarditis

7. Non-steroidal anti-inflammatory therapy is recommended in mild cases **(BIII)**.
8. Prednisone 0.5 to 1.0 mg/kg/d (maximum 80 mg daily) in tapering doses over 1 to 2 weeks is recommended in patients with evidence for hemodynamic compromise or unremitting symptoms after several days of therapy with non-steroidal anti-inflammatory therapy **(BIII)**.
9. Pericardial fluid removal is indicated in patients with hemodynamic compromise **(AIII)**.
10. Itraconazole, 200 mg 3 times daily for 3 days and then once or twice daily for 6 to 12 weeks is recommended if corticosteroids are administered **(BIII)**.

Rheumatologic Syndromes

11. Non-steroidal anti-inflammatory therapy is recommended in mild cases **(BIII)**.

12. Prednisone 0.5 to 1.0 mg/kg/d (maximum 80 mg daily) in tapering doses over 1 to 2 weeks is recommended in severe cases **(BIII)**.
13. Itraconazole, 200 mg 3 times daily for 3 days and then once or twice daily for 6 to 12 weeks is recommended only if corticosteroids are administered **(BIII)**.

Mediastinal Lymphadenitis

14. Treatment is usually unnecessary **(AIII)**.
15. Itraconazole, 200 mg 3 times daily for 3 days and then 200 mg once or twice daily, for 6 to 12 weeks is recommended in patients who have symptoms that warrant treatment with corticosteroids and in those who continue to have symptoms for longer than a month **(BIII)**.
16. Prednisone 0.5 to 1.0 mg/kg/d (maximum 80 mg daily) in tapering doses over 1 to 2 weeks is recommended in severe cases with obstruction or compression of contiguous structures. **(BIII)**.

Mediastinal Granuloma

17. Treatment is usually unnecessary **(AIII)**.
18. Itraconazole, 200 mg 3 times daily for 3 days and then once or twice daily for 6 to 12 weeks is recommended for symptomatic cases **(BIII)**.

Mediastinal Fibrosis

19. Antifungal treatment is not recommended **(AIII)**.
20. The placement of intravascular stents is recommended for selected patients with pulmonary vessel obstruction **(BIII)**.
21. Itraconazole, 200 mg once or twice daily, for 12 weeks is recommended if clinical findings cannot differentiate mediastinal fibrosis from mediastinal granuloma **(CIII)**.

Broncholithiasis

22. Antifungal treatment is not recommended **(AIII)**.
23. Bronchoscopic or surgical removal of the broncholith is recommended **(AIII)**.

Pulmonary Nodules (Histoplasmomas)

24. Antifungal treatment is not recommended **(AIII)**.

What Is the Treatment for Progressive Disseminated Histoplasmosis?

25. For moderately severe to severe disease, liposomal amphotericin B, 3.0 mg/kg/d is recommended for 1 to 2 weeks, followed by oral itraconazole, 200 mg 3 times daily for 3 days and then 200 mg twice daily for a total of at least 12 months **(AI)**.
26. Substitution of another lipid formulation, at a dosage of 5.0 mg/kg/d, may be preferred in some patients because of cost or tolerability **(AIII)**.

27. The deoxycholate formulation of amphotericin B 0.7 to 1.0 mg/kg/d is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity **(AIII)**.
28. For mild to moderate disease, itraconazole, 200 mg 3 times daily for 3 days and then twice daily for at least 12 months is recommended **(AII)**.
29. Lifelong suppressive therapy with itraconazole 200 mg daily, may be required in immunosuppressed patients if immunosuppression cannot be reversed **(AII)**, and in patients who relapse despite appropriate therapy **(CIII)**.
30. Blood levels of itraconazole should be obtained to ensure adequate drug exposure **(BIII)**.
31. Antigen levels should be measured during therapy and for 12 months after therapy is ended to monitor for relapse **(BIII)**. Persistent low-level antigenuria may not be a reason to prolong treatment in patients who have completed appropriate therapy and have no evidence for active infection.

Is Prophylaxis Recommended for Immunosuppressed Patients?

32. Prophylaxis with itraconazole 200 mg daily is recommended in patients with HIV infection with CD4 counts <150 cells/mm^3 in specific endemic areas in which the incidence of histoplasmosis is >10 cases per 100 patient years **(AI)**.
33. Prophylaxis with itraconazole 200 mg daily may be appropriate in specific circumstances in other immunosuppressed patients **(CIII)**.

What Is the Treatment for Central Nervous System Histoplasmosis?

34. Liposomal amphotericin B, 5.0 mg/kg/d for total of 175 mg/kg given over 4 to 6 weeks followed by itraconazole, 200 mg 2 or 3 times daily for at least one year and until resolution of cerebrospinal fluid abnormalities, including *Histoplasma* antigen levels, is recommended **(BIII)**.
35. Blood levels of itraconazole should be obtained to ensure adequate drug exposure **(BIII)**.

What Is the Treatment for Histoplasmosis in Pregnancy?

36. Lipid formulation amphotericin B, 3.0 to 5.0 mg/kg/d, for 4 to 6 weeks is recommended **(AIII)**.
37. The deoxycholate formulation of amphotericin B, 0.7 to 1.0 mg/kg/d is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity **(AIII)**.
38. If the newborn shows evidence for infection, treatment is recommended with amphotericin B deoxycholate 1.0 mg/kg/d for 4 weeks **(AIII)**.

What Treatment Is Recommended for Histoplasmosis in Children?

Acute Pulmonary Histoplasmosis

39. Treatment indications and regimens are similar to adults, except that amphotericin B deoxycholate, 1.0 mg/kg/d is usually well tolerated, and the lipid preparations are not preferred **(AIII)**.

40. Itraconazole dosage in children is 5.0 to 10.0 mg/kg/d in two divided doses, not to exceed 400 mg daily, generally using the solution formulation **(AIII)**.

Progressive Disseminated Histoplasmosis

41. Amphotericin B deoxycholate, 1.0 mg/kg/d for 4 to 6 weeks is recommended **(AIII)**
42. Amphotericin B deoxycholate, 1.0 mg/kg/d for 2 to 4 weeks, followed by itraconazole 5.0 to 10.0 mg/kg/d in two divided doses, not to exceed 400 mg daily, to complete 3 months of therapy is an alternative **(AIII)**.
43. Longer therapy may be needed in patients with severe disease, immunosuppression or primary immunodeficiency syndromes **(AIII)**.
44. Lifelong suppressive therapy with itraconazole 5.0 mg/kg/d up to 200 mg daily, may be required in immunosuppressed patients if immunosuppression cannot be reversed **(AII)**, and in patients who relapse despite appropriate therapy **(CIII)**.
45. Blood levels of itraconazole should be obtained to ensure adequate drug exposure **(BIII)**.
46. Antigen levels should be monitored during therapy and for 12 months after therapy is ended to monitor for relapse **(BIII)**. Persistent low-level antigenuria may not be a reason to prolong treatment in patients who have completed appropriate therapy and have no evidence for active infection.

Performance Measures

1. Itraconazole is the preferred azole for initial therapy of patients with mild to moderate histoplasmosis and as step-down therapy after amphotericin B. When other azole agents are used, the medical record should document the specific reasons that itraconazole was not used and why other azoles were used.
2. Patients with severe or moderately severe histoplasmosis should be treated with an amphotericin B formulation initially. When amphotericin B is used, the patient's electrolytes, renal function, and blood counts should be monitored several times a week and documented in the medical record.
3. Itraconazole drug levels should be measured during the first month in patients with disseminated or chronic pulmonary histoplasmosis and these levels should be documented in the medical record, as well as the physician's response to levels that are too low.
4. Itraconazole should not be given to patients receiving the contraindicated medications: pimozide, quinidine, dofetilide, lovastatin, simvastatin, midazolam, triazolam. Reasons for deviation from this practice should be documented in the medical record.

Definitions:

Quality of Evidence

I. Evidence from ≥1 properly randomized, controlled trial
II. Evidence from ≥ well-designed clinical trial without randomization, from cohort or case-control analytic studies (preferably from ≥ center), from multiple time-series, or from dramatic results from uncontrolled experiments

III. Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Strength of Recommendation

A. Good evidence to support a recommendation for use
B. Moderate evidence to support a recommendation for use
C. Poor evidence to support a recommendation

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate management of patients with histoplasmosis

POTENTIAL HARMS

Adverse Effects of Medications

- *Amphotericin B deoxycholate* is associated with nephrotoxicity.
- *Itraconazole* solution can cause unacceptable gastrointestinal side effects, reducing adherence to therapy.
- *Fluconazole* is associated with development of resistance.
- Drug-drug interactions are common and vary with each *azole*. Additionally, *azoles* may be hepatotoxic.
- *Corticosteroids* can induce immunosuppression

CONTRAINDICATIONS

CONTRAINDICATIONS

- All *azoles* are contraindicated in pregnancy because of the risk of teratogenicity.
- *Itraconazole* should not be given to patients receiving the contraindicated medications: pimozide, quinidine, dofetilide, lovastatin, simvastatin, midazolam, triazolam.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. Infectious Diseases Society of America (IDSA) considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Wheat LJ, Freifeld AG, Kleiman MB, Baddley JW, McKinsey DS, Loyd JE, Kauffman CA, Infectious Diseases Society of America. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis 2007 Oct 1;45(7):807-25. [105 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000 Apr (revised 2007 Oct)

GUIDELINE DEVELOPER(S)

Infectious Diseases Society of America - Medical Specialty Society

SOURCE(S) OF FUNDING

Infectious Diseases Society of America (IDSA)

GUIDELINE COMMITTEE

Infectious Diseases Society of America (IDSA) Standards and Practice Guidelines Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

LJW is President of MiraVista Diagnostics and MiraBella Technologies. He has research contracts with Astellas, Basilea, Schering-Plough and Bio-Rad Laboratories and serves as a consultant to Bio-Rad Laboratories. LJW is also a speaker for Bio-Rad and Enzon.

JWB has research grants with Merck and Astellas, and is on the speaker bureaus for Merck, Pfizer and Enzon.

AGF serves as a consultant for Enzon and a speaker for Pfizer, Merck and Schering.

CAK holds research grants with Merck, Astellas and Schering-Plough and is on the speaker bureaus for Merck, Pfizer, Astellas and Schering-Plough.

DSM is on the speaker bureaus of Merck and Pfizer.

MBK and JEL: no potential conflicts.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Wheat J, Sarosi G, McKinsey D, Hamill R, Bradsher R, Johnson P, Loyd J, Kauffman C. Practice guidelines for the management of patients with histoplasmosis. Infectious Diseases Society of America. Clin Infect Dis 2000 Apr;30(4):688-95.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Infectious Diseases Society (IDSA) Web site.

Print copies: Available from Dr. L. Joseph Wheat, MiraVista Diagnostics/MiraBella Technologies, 4444 Decatur Blvd., Ste. 300, Indianapolis, IN 46241, Email: jwheat@miravistalabs.com.

AVAILABILITY OF COMPANION DOCUMENTS

A PDA version of the original guideline document is available from www.idsaguidelinesforhandhelds.org.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on May 1, 2001. The information was verified by the guideline developer as of June 29, 2001. This summary was updated on May 3, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisory on COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This NGC summary was updated by ECRI Institute on October 25, 2007. The updated information was verified by the guideline developer on November 8, 2007.

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Date Modified: 9/22/2008